CLAIMS

What is claimed is:

1. Ion channel modulating compounds that block cardiac early repolarising currents and cardiac sodium currents.

2. Ion channel modulating compounds according to claim 1 that block the cardiac ion channels responsible for early repolarising currents and sodium currents.

3. Ion channel modulating compounds according to claim 1 that block cardiac early repolarising currents and cardiac sodium currents under conditions where an arrhythmogenic substrate is present in the heart.

4. Ion channel modulating compounds according to claim 1 that block the cardiac ion channels responsible for early repolarising currents and sodium currents under conditions where an arrhythmogenic substrate is present in the heart.

5. Ion channel modulating compounds according to claim 1 that block cardiac early repolarising currents and cardiac sodium currents from extracellular loci in cardiac cells.

6. Ion channel modulating compounds according to claim 1 wherein the ion channel modulating compounds have pKa values of between 4-9.

7. Ion channel modulating compounds according to claim 1 wherein the ion channel modulating compounds have pKa values of between 5-7.5.

8. Ion channel modulating compounds according to claim 1 wherein the cardiac early repolarising currents comprise ionic currents which activate rapidly after depolarisation of membrane voltage and which effect repolarisation of the cell.

9. Ion channel modulating compounds according to claim 1 wherein the early repolarising currents comprise the cardiac transient outward potassium current (I_{to}) and/or the ultrarapid delay rectifier current (I_{Kur}).

10. Ion channel modulating compounds according to claim 9 wherein the cardiac transient outward potassium current (I_{to}) and/or the ultrarapid delay rectifier current (I_{Kur}) comprise at least one of the Kv4.2, Kv4.3, Kv2.1, Kv1.4 and Kv1.5 currents.

11. A composition comprising one or more ion channel modulating compounds according to claim 1 in combination with a pharmaceutically acceptable carrier, excipient or diluent.

12. A compound or composition according to any one of claims 1 or 11 for use in a method for treating or preventing arrhythmia in a warm-blooded animal.

13. A compound or composition according to any one of claims 1 or 11 for use in a method for modulating ion channel activity in a warm-blooded animal.

14. A compound or composition according to any one of claims 1 or 11 for use in a method for modulating ion channel activity *in vitro*.

15. Use of a compound according to claim 1 in a manufacture of a medicament.

16. A pharmaceutical composition comprising an amount of a compound according to claim 1 effective to treat or prevent atrial arrhythmia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

17. A method for treating or preventing atrial arrhythmia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 1 or a composition according to claim 16.

18. A pharmaceutical composition comprising an amount of a compound according to claim 1 effective to treat or prevent ventricular arrhythmia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

19. A method for treating or preventing ventricular arrhythmia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 1 or a composition according to claim 18.

20. A method for inhibiting multiple cardiac ionic current, comprising administering to a warm-blooded animal in need thereof one or more compounds that either singly or together both block cardiac early repolarising currents and cardiac sodium currents, said one or more compounds being administered in an amount effective to block cardiac sodium currents and cardiac early repolarising currents.

21. A method according to claim 20 wherein said one or more compounds either singly or together both block cardiac early repolarising currents and cardiac sodium currents from extracellular loci in cardiac cells.

22. A method for inhibiting multiple cardiac ionic currents, comprising administering to a warm-blooded animal in need thereof one or more compounds that either singly or together both block the cardiac ion channels responsible for early repolarising currents and sodium channels, said one or more compounds being administered in an amount effective to block the cardiac sodium ion channels and the cardiac early repolarising ion channels.

23. A method according to claim 22 wherein said one or more compounds either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells.

24. A method according to claim 20 wherein one compound blocks both sodium currents and cardiac early repolarising currents from extracellular loci in cardiac cells.

25. A method according to claim 20 wherein each of said one or more compounds has a pKa value of less than 8.

26. A method for treating or preventing a cardiac condition wherein there is an "arrhythmogenic substrate" present in the heart, comprising administering to a warm-blooded animal in need thereof, an amount effective to treat or prevent said cardiac condition, one or more compounds that either singly or together block cardiac early repolarising currents and cardiac sodium currents.

27. A method according to claim 26 wherein said one or more compounds either singly or together both block cardiac early repolarising currents and cardiac sodium currents from extracellular loci in cardiac cells.

28. A method according to claim 26 wherein one compound both blocks cardiac early repolarising currents and cardiac sodium currents from extracellular loci in cardiac cells.

29. A method according to claim 26 wherein each of said one or more compounds has a pKa value of less than 8.

30. A method for treating or preventing a cardiac condition wherein there is an "arrhythmogenic substrate" present in the heart, comprising administering to a warm-blooded animal in need thereof, an amount effective to treat or prevent said cardiac condition, one or more compounds that either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents.

31. A method according to claim 30 wherein said one or more compounds either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells.

32. A method according to claim 30 wherein one compound both blocks cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells.

33. A method according to claim 30 wherein each of said one or more compounds has a pKa value of less than 8.

34. A method for treating or preventing a cardiac condition wherein there is an increase in acidity of the cardiac milieu from the normal physiological pH of the milieu, comprising administering to a warm-blooded animal in need thereof, an amount effective to treat or prevent said cardiac condition, one or more compounds that either singly or together both block cardiac early repolarising currents and cardiac sodium currents.

35. A method according to claim 34 wherein said one or more compounds either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells.

36. A method according to claim 34 wherein one compound both blocks cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells.

37. A method according to claim 34 wherein each of said one or more compounds has a pKa value of less than 8.

38. A method for treating or preventing a cardiac condition wherein there is an increase in acidity of the cardiac milieu from the normal physiological pH of the milieu, comprising administering to a warm-blooded animal in need thereof, an amount effective to treat or prevent said cardiac condition, one or more compounds that either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents.

39. A method according to claim 38 wherein said one or more compounds either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells.

40. A method according to claim 38 wherein one compound both blocks cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells.

41. A method according to claim 38 wherein each of said one or more compounds has a pKa value of less than 8.

42. A method according to any one of claims 26, 30, 34 or 38 wherein the cardiac condition is ventricular arrhythmia.

43. A method according to any one of claims 26, 30, 34 or 38 wherein the cardiac condition is atrial arrhythmia.

44. A method according to claims 34 or 38 wherein the increase in acidity of the cardiac milieu is due to myocardial ischaemia.

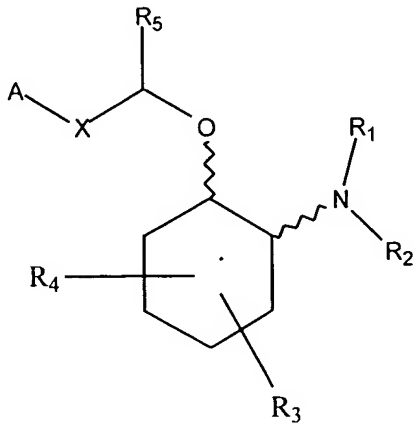
45. A method according to claims 34 or 38 wherein increase in acidity of the cardiac milieu is due to high heart rate.

46. A method according to claims 34 or 38 wherein the increase in acidity is due to inflammation.

47. A method according to claims 34 or 38 wherein the increase in acidity is due to the presence of an arrhythmogenic substrate in the heart.

48. A method according to claims 34 or 38 wherein the increase in acidity is due to conditions which precede atrial fibrillation.

49. A compound of formula (I), or a solvate or pharmaceutically acceptable salt thereof:



(I)

wherein, independently at each occurrence,

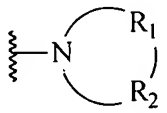
X is selected from a direct bond, -C(R_6,R_{14})-Y-, and -C(R_{13})=CH-, with the proviso that when X is a direct bond and A is formula (III) then at least one of R_7, R_8 and R_9 is not hydrogen;

Y is selected from a direct bond, O, S, and C_1-C_4alkylene;

R_{13} is selected from hydrogen, C_1-C_6alkyl, C_3-C_8cycloalkyl, aryl, and benzyl;

R_1 and R_2 are independently selected from hydrogen, C_1-C_8alkyl, C_3-C_8alkoxyalkyl, C_1-C_8hydroxyalkyl, and C_7-C_{12}aralkyl; or

R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (I), form a ring denoted by formula (II):



(II)

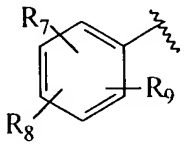
wherein the ring of formula (II) is formed from the nitrogen as shown as well as three to nine additional ring atoms independently selected from carbon, nitrogen, oxygen, and sulfur; where any two adjacent ring atoms may be joined together by single or double bonds, and where any one or more of the additional carbon ring atoms may be substituted with one or two substituents selected from hydrogen, hydroxy, C_1-C_3hydroxyalkyl, oxo, C_2-C_4acyl, C_1-C_3alkyl, C_2-C_4alkylcarboxy, C_1-C_3alkoxy, C_1-C_{20}alkanoyloxy, or may be substituted to form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur; and any two adjacent additional carbon ring atoms may be fused to a C_3-C_8carbocyclic ring, and any one or more of the additional nitrogen ring atoms may be substituted with substituents selected from hydrogen, C_1-C_6alkyl, C_2-C_4acyl, C_2-C_4hydroxyalkyl and C_3-C_8alkoxyalkyl; or

R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (I), may form a bicyclic ring system selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, and 3-azabicyclo[3.2.0]heptan-3-yl;

R_3 and R_4 are independently attached to the cyclohexane ring shown in formula (I) at the 3-, 4-, 5- or 6- positions and are independently selected from hydrogen, hydroxy, C_1-C_6alkyl, and C_1-C_6alkoxy, and, when both R_3 and R_4 are attached to the same cyclohexane ring atom, may together form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur;

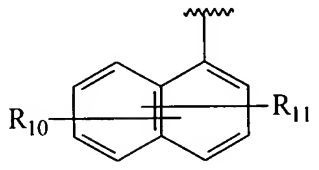
R_5, R_6 and R_{14} are independently selected from hydrogen, C_1-C_6alkyl, aryl and benzyl, or R_6 and R_{14}, when taken together with the carbon to which they are attached, may form a spiro C_3-C_5cycloalkyl;

A is selected from C_5-C_{12}alkyl, a C_3-C_{13}carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII) and (VIII):



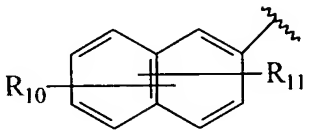
(III)

where R_7, R_8 and R_9 are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7alkanoyloxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-C_7alkoxycarbonyl, C_1-C_6thioalkyl and $N(R_{15},R_{16})$ where R_{15} and R_{16} are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1-C_6alkyl;



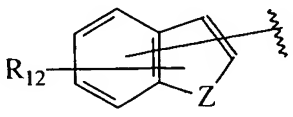
(IV)

and



(V)

where R_{10} and R_{11} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7alkanoyloxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-C_7alkoxycarbonyl, C_1-C_6thioalkyl, and $N(R_{15},R_{16})$ where R_{15} and R_{16} are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1-C_6alkyl;



(VI)

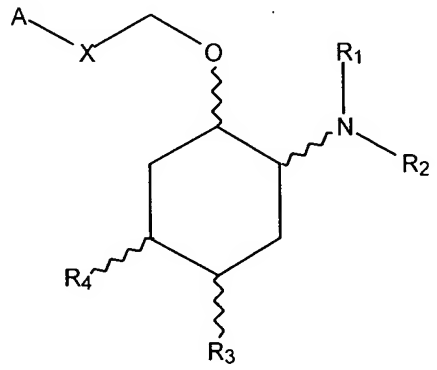
X is selected from a direct bond, -C(R_6,R_{14})-Y-, and -C(R_{13})=CH-, with the proviso that when X is a direct bond and A is formula (III) then at least one of R_7, R_8 and R_9 is not hydrogen;

Y is selected from a direct bond, O and S; and

R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, A and Z are defined as in claim 49;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

51. A compound of claim 49 having formula (X), or a solvate or pharmaceutically acceptable salt thereof:



(X)

wherein, independently at each occurrence,

X is selected from a direct bond, -C(R_6,R_{14})-Y-, and -C(R_{13})=CH-, with the proviso that when X is a direct bond and A is formula (III) then at least one of R_7, R_8 and R_9 is not hydrogen;

Y is selected from a direct bond, O, and S;

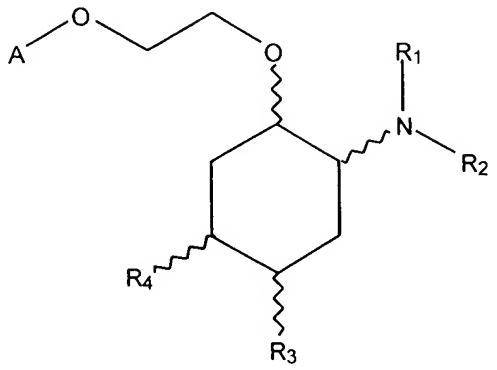
R_1, R_2, R_6 and R_{14} are defined as in claim 49;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and C_1-C_6alkoxy; and

A is selected from C_5-C_{12}alkyl, C_3-C_8cycloalkyl, and any of formulae (III), (IV), (V), and (VI) as defined in claim 49, wherein Z, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are defined as in claim 49;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

52. A compound of claim 49 having formula (XI), or a solvate or pharmaceutically acceptable salt thereof:



(XI)

wherein, independently at each occurrence,

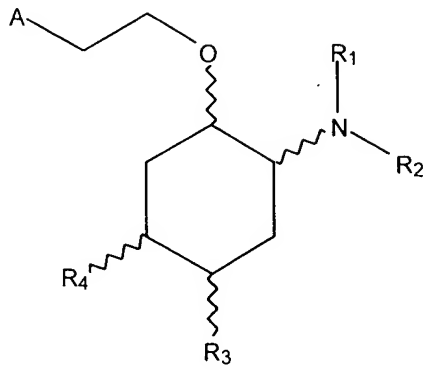
R_1 and R_2 are defined as in claim 49;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from C_5-C_{12}alkyl, C_3-C_8cycloalkyl, and any of formulae (III), (IV), (V), and (VI) as defined in claim 49, wherein Z, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are defined as in claim 49;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

53. A compound of claim 49 having formula (XII), or a solvate or pharmaceutically acceptable salt thereof:



(XII)

wherein, independently at each occurrence,

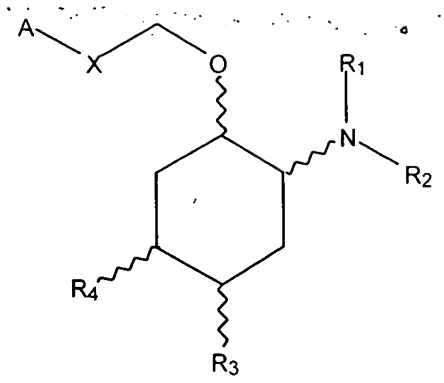
R_1 and R_2 are defined as in claim 49;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from C_5-C_{12}alkyl, C_3-C_8cycloalkyl, and any of formulae (III), (IV), (V) and (VI) as defined in claim 49, wherein Z, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are defined as in claim 49;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

54. A compound of claim 49 having formula (XIII), or a solvate or pharmaceutically acceptable salt thereof:



(XIII)

wherein, independently at each occurrence,

X is selected from -C(R_6,R_{14})-Y- and -CH=CH-;

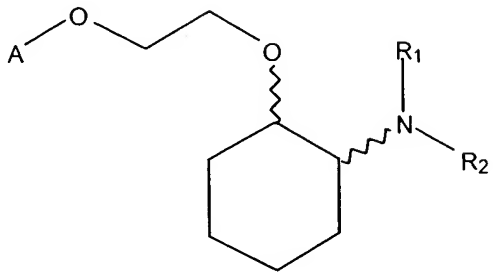
Y, R_1, R_2, R_6 and R_{14} are defined as in claim 49;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from C_3-C_8cycloalkyl and any of formulae (III), (IV), (V), (VI), (VII) and (VIII) as defined in claim 49, where R_8 and R_9 are defined as in claim 49, R_7, R_{10}, R_{11} and R_{12} are hydrogen, and Z is selected from O, S and N-R_{17} where R_{17} is selected from hydrogen and methyl;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

55. A compound of claim 49 having formula (XIV), or a solvate or pharmaceutically acceptable salt thereof:



(XIV)

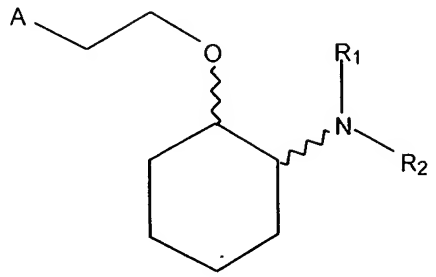
wherein, independently at each occurrence,

R_1 and R_2 are defined as in claim 49; and

A is selected from any of formulae (III), (IV), (V) and (VI) as defined in claim 49, wherein R_7, R_{10}, R_{11} and R_{12} are hydrogen, R_8 and R_9 are independently selected from hydrogen, hydroxy, fluorine, chlorine, bromine, methanesulfonamido, methanoyloxy, methoxycarbonyl, nitro, sulfamyl, thiomethyl, trifluoromethyl, methyl, ethyl, methoxy, ethoxy and NH_2, with the proviso that at least one of R_8 and R_9 is not hydrogen; and Z is selected from O and S;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

56. A compound of claim 49 having formula (XV), or a solvate or pharmaceutically acceptable salt thereof:



(XV)

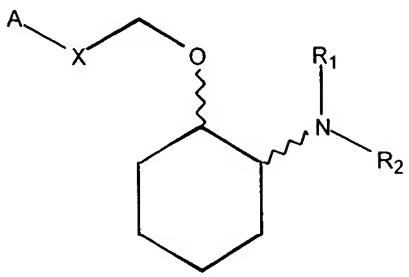
wherein, independently at each occurrence,

R_1 and R_2 are defined as in claim 49; and

A is selected from any of formulae (III), (IV), (V) and (VI) as defined in claim 49, wherein R_7, R_{10}, R_{11} and R_{12} are hydrogen, R_8 and R_9 are independently selected from hydrogen, hydroxy, fluorine, chlorine, bromine, methanesulfonamido, methanoyloxy, methoxycarbonyl, nitro, sulfamyl, thiomethyl, trifluoromethyl, methyl, ethyl, methoxy, ethoxy and NH_2, with the proviso that at least one of R_8 and R_9 is not hydrogen; and Z is selected from O and S;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

57. A compound of claim 49 having formula (XVI), or a solvate or pharmaceutically acceptable salt thereof:



(XVI)

wherein, independently at each occurrence,

X is selected from a direct bond, *trans*-CH=CH-, $-CH_2-$ and $-CH_2-O-$;

R_1 and R_2 are both methoxyethyl or, when taken together with the nitrogen atom to which they are attached, complete a ring selected from pyrrolidinyl, 2-ketopyrrolidinyl, 3-ketopyrrolidinyl, 2-acetoxypyrrolidinyl, 3-acetoxypyrrolidinyl, 2-hydroxypyrrolidinyl, 3-hydroxypyrrolidinyl, thiazolidinyl, piperidinyl, 2-ketopiperidinyl, 3-ketopiperidinyl, 4-ketopiperidinyl,acetylpiperazinyl, 1,4-dioxa-7-azaspiro[4.4]non-7-yl, hexahydroazepinyl, morpholinyl, N-methylpiperazinyl and 3-azabicyclo[3.2.2]nonanyl; and

A is selected from cyclohexyl, monochlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 2-bromophenyl, 2,4-dibromophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dimethoxyphenyl, 1-naphthyl, 2-naphthyl, 3-benzo(b)thiophenyl, 4-benzo(b)thiophenyl, (2-trifluoromethyl)phenyl, 2,4-di(trifluoromethyl)phenyl, and (4-trifluoromethyl)phenyl.

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

58. A compound, or mixture comprising compounds, selected from the group consisting of:

(+)-*trans*-[2-(4-morpholinyl)-1-(2-naphthenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(2-naphthenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(1-naphthenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(1-naphthenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(4-bromophenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(4-bromophenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-[2-(2-naphthoxy)ethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-[2-(2-naphthoxy)ethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-[2-(4-bromophenoxy)ethoxy]]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-[2-(4-bromophenoxy)ethoxy]]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(3,4-dimethoxyphenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(3,4-dimethoxyphenethoxy)]cyclohexane;

(+)-*trans*-[2-(1-pyrrolidinyl)-1-(1-naphthenethoxy)]cyclohexane;

(-)-*trans*-[2-(1-pyrrolidinyl)-1-(1-naphthenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-3-yl)ethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-3-yl)ethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-4-yl)ethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-4-yl)ethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(3-bromophenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(3-bromophenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(2-bromophenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(2-bromophenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(3-(3,4-dimethoxyphenyl)-1-propoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(3-(3,4-dimethoxyphenyl)-1-propoxy)]cyclohexane;

(+)-*trans*-[2-[bis(2-methoxyethyl)aminyl]-1-(2-naphthenethoxy)]cyclohexane;

(-)-*trans*-[2-[bis(2-methoxyethyl)aminyl]-1-(2-naphthenethoxy)]cyclohexane;

(1R,2R)/(1S,2S)-2-(4-morpholinyl)-1-(3,4-dichlorophenethoxy)cyclohexane;

(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane;

(1R,2R)/(1S,2S)-2-(1-acetylpiperazinyl)-1-(2-naphthenethoxy)cyclohexane;

(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane;

(1R,2R)/(1S,2S)-2-[1,4-dioxa-7-azaspiro[4.4]non-7-yl]-1-(1-naphthenethoxy)cyclohexane;

(1R,2S)/(1S,2R)-2-(4-morpholinyl)-1-[(2-trifluoromethyl)phenethoxy]cyclohexane;

(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-[3-(cyclohexyl)propoxy]cyclohexane;

(1R,2R)/(1S,2S)-2-(3-acetoxypyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane;

(1R,2R)/(1S,2S)-2-(4-morpholinyl)-1-[(2,6-dichlorophenyl)methoxy]cyclohexane;

(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-[(2,6-dichlorophenyl)methoxy]cyclohexane;

(1R,2R)/(1S,2S)-2-(3-hydroxypyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane;

(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(2,2-diphenylethoxy)cyclohexane;

(1R,2R)/(1S,2S)-2-(3-thiazolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane;

(1R,2S)/(1S,2R)-2-(3-ketopyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane; and

(1R,2R)/(1S,2S)-2-(3-hydroxypyrrolidinyl)-1-(3,4-dimethoxyphenethoxy)cyclohexane;

including isolated enantiomeric and diastereomeric isomers thereof, and mixtures thereof; and pharmaceutically acceptable salts thereof.

59. A composition comprising a compound according to claim 49 in combination with a pharmaceutically acceptable carrier, excipient or diluent.

60. Use of a compound according to claim 49 in a manufacture of a medicament.

61. A compound or composition according to claim 49 for use in a method for treating or preventing arrhythmia in a warm-blooded animal.

62. A compound or composition according to claim 49 for use in a method for modulating ion channel activity in a warm-blooded animal.

63. A compound or composition according to claims 49 or 59 for use in a method for modulating ion channel activity *in vitro*.

64. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent diseases of the central nervous system in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

65. A method for treating or preventing diseases of the central nervous system in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 64.

66. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent convulsion in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

67. A method for treating or preventing convulsion in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 66.

68. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent epileptic spasms in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

69. A method for treating or preventing epileptic spasms in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 68.

70. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent depression, anxiety or schizophrenia, in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

71. A method for treating or preventing depression, anxiety or schizophrenia, in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 70.

72. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent Parkinson's disease in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

73. A method for treating or preventing Parkinson's disease in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 72.

74. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent respiratory disorders in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

75. A method for treating or preventing respiratory disorders in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 74.

76. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent cystic fibrosis in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

77. A method for treating or preventing cystic fibrosis in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 76.

78. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent asthma in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

79. A method for treating or preventing asthma in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 78.

80. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent a cough in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

81. A method for treating or preventing a cough in a warm-blooded animal comprising administration of a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 80.

82. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent inflammation in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

83. A method for treating or preventing inflammation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 82.

84. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent arthritis in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

85. A method for treating or preventing arthritis in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 84.

86. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent allergies in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

87. A method for treating or preventing allergies in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 86.

88. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent gastrointestinal disorders in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

89. A method for treating or preventing gastrointestinal disorders in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 88.

90. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent urinary incontinence in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

91. A method for treating or preventing urinary incontinence in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 90.

92. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent irritable bowel syndrome in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

93. A method for treating or preventing irritable bowel syndrome in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 92.

94. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent cardiovascular diseases in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

95. A method for treating or preventing cardiovascular diseases in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 94.

96. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent cerebral or myocardial ischemias in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

97. A method for treating or preventing cerebral or myocardial ischemias in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 96.

98. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent hypertension in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

99. A method for treating or preventing hypertension in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 98.

100. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent long-QT syndrome in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

101. A method for treating or preventing long-QT syndrome in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 100.

102. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent stroke in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

103. A method for treating or preventing stroke in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 102.

104. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent migraine in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

105. A method for treating or preventing migraine in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 104.

106. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent ophthalmic diseases in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

107. A method for treating or preventing ophthalmic diseases in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 106.

108. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent diabetes mellitus in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

109. A method for treating or preventing diabetes mellitus in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 108.

110. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent myopathies in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

111. A method for treating or preventing myopathies in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 110.

112. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent Becker's myotonia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

113. A method for treating or preventing Becker's myotonia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 112.

114. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent myasthenia gravis in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

115. A method for treating or preventing myasthenia gravis in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 114.

116. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent paramyotonia congentia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

117. A method for treating or preventing paramyotonia congentia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 116.

118. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent malignant hyperthermia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

119. A method for treating or preventing malignant hyperthermia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 118.

120. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent hyperkalemic periodic paralysis in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

121. A method for treating or preventing hyperkalemic periodic paralysis in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 120.

122. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent Thomsen's myotonia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

123. A method for treating or preventing Thomsen's myotonia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 122.

124. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent autoimmune disorders in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

125. A method for treating or preventing autoimmune disorders in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 124.

126. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent graft rejection in organ transplantation or bone marrow transplantation in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

127. A method for treating or preventing graft rejection in organ transplantation or bone marrow transplantation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 126.

128. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to produce local analgesia or anesthesia in a warm-blooded animal in need thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

129. A method for producing local analgesia or anesthesia in a warm-blooded animal in need thereof comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 128.

130. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent heart failure in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

131. A method for treating or preventing heart failure in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 130.

132. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent hypotension in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

133. A method for treating or preventing hypotension in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 132.

134. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent Alzheimer's disease in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

135. A method for treating or preventing Alzheimer's disease in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 134.

136. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent dementia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

137. A method for treating or preventing dementia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 136.

138. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent alopecia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

139. A method for treating or preventing alopecia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 138.

140. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to enhance libido in a warm-blooded animal in need thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

141. A method for enhancing libido in a warm-blooded animal in need thereof comprising administering to a warm-blooded animal in need thereof an enhancing amount of a compound according to claim 49 or a composition according to claim 140.

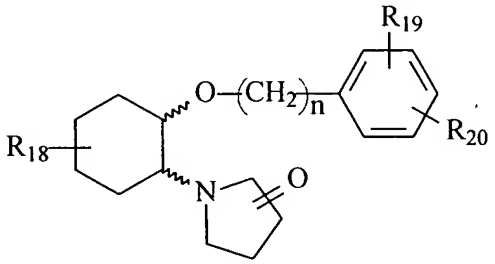
142. A compound or composition according to claims 49 or 59 for use in a method for treating or preventing atrial arrhythmia in a warm-blooded animal.

143. A compound or composition according to claims 49 or 59 for use in a method for treating or preventing ventricular arrhythmia in a warm-blooded animal.

144. A compound or composition according to claims 49 or 59 for use in a method for treating or preventing atrial fibrillation in a warm-blooded animal.

145. A compound or composition according to claims 49 or 59 for use in a method for treating or preventing ventricular fibrillation in a warm-blooded animal.

146. A compound of formula (XVII), or a solvate or pharmaceutically acceptable salt thereof:



(XVII)

wherein, independently at each occurrence,

n is selected from 1, 2 and 3;

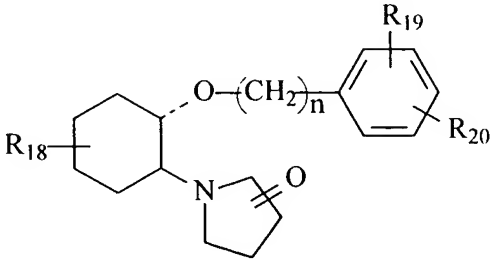
R_{18} is either hydrogen or methyl and is independently attached to the cyclohexane ring shown in formula (XVII) at one of the 3-, 4-, 5- or 6- positions;

R_{19} is selected from a group consisting of bromine, chlorine, fluorine and hydrogen; and

R_{20} is selected from a group consisting of bromine, chlorine and fluorine;

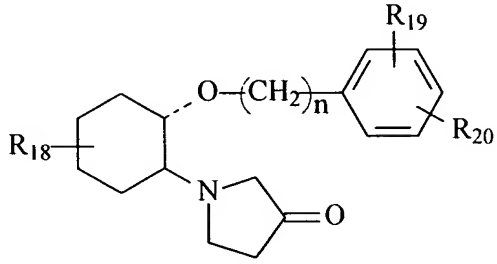
including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

147. A compound according to claim 146, having a *trans* configuration as represented by formula (XVIII):



(XVIII).

148. A compound according to claim 146, wherein the keto function is at the C3 position of the pyrrolidine ring as represented by formula (IXX):



(IXX).

149. A compound according to claims 146, 147 or 148, wherein n is 2.

150. A compound according to claims 146, 147 or 148, wherein R_{18} is hydrogen.

151. A compound according to claims 146, 147 or 148, wherein R_{19} is hydrogen.

152. A compound according to claims 146, 147 or 148, wherein R_{19} is chlorine.

153. A compound according to claims 146, 147 or 148, wherein R_{20} is chlorine.

154. A compound according to claims 146, 147 or 148, wherein n is 2; R_{18} is hydrogen; R_{19} is chlorine; and R_{20} is chlorine.

155. A compound according to claim 154, wherein R_{19} is chlorine at C2 of phenyl group; and R_{20} is chlorine at C6 of phenyl group.

156. A compound according to claim 147, wherein n is 2; R_{18} is hydrogen; R_{19} is chlorine at C2 of phenyl group; and R_{20} is chlorine at C6 of phenyl group.

157. A racemate which is (1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane and pharmaceutically acceptable salts thereof.

158. A compound which is (1R,2R)-2-(3-ketopyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane and pharmaceutically acceptable salts thereof.

159. A compound which is (1S,2S)-2-(3-ketopyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane and pharmaceutically acceptable salts thereof.